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EXAMINER	
HAMUD, FOZIA M	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/749,699	STROM ET AL.	
	Examiner	Art Unit	
	Fozia M. Hamud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 35-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 35-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1a. Receipt of Applicants' amendment and arguments, filed on 23 October 2006 is acknowledged.

Status of Claims:

1b. New claims 35-46 have been added, thus claims 1 and 35-46 are pending and under consideration.

Response to Applicants' arguments:

Maintenance of Previous Rejections:

Claim rejections-35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2a. Claims 1, 35-36 and 42-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a mutant of IL-15, said mutant having mutations at positions 149 and 156 of the wild type IL-15, wherein a glutamine is replaced with an aspartic acid, fused to the Fc region of immunoglobulin, or a composition comprising IL-2 fused to the Fc region of immunoglobulin, does not reasonably provide enablement for a therapeutic composition comprising a first agent that comprises "all possible" mutant IL-15 polypeptides that bind to an IL-15R but fails to fully activate signal transduction, optionally fused to the Fc region of an immunoglobulin, and a second agent that comprises an IL-2 polypeptide

that is optionally fused to the Fc region of an immunoglobulin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims 1 and 45 are drawn to a therapeutic composition comprising a first agent that comprises/consists a mutant IL-15 polypeptide that binds to an IL-15R but fails to fully activate signal transduction, optionally fused to the Fc region of an immunoglobulin, and a second agent that comprises/consists an IL-2 polypeptide that is optionally fused to the Fc region of an immunoglobulin. The instant specification discloses a mutant of IL-15, said mutant having mutations at positions 149 and 156 of the wild type IL-15, wherein a glutamine is replaced with an aspartic acid, fused to Fc, (an IL-15 receptor antagonist). Prior art discloses the same IL-15 mutant/FC chimera that binds to IL-15R but fails to support the proliferation of IL-15 sensitive IL2Rβ$^+$ BAF-BO3 cells, (see Kim et al page 5744, column 2). The instant specification also discloses a lytic IL-2/Fc molecule which lyses IL-2R bearing CTLL-2 cells, (see page 46-47). However, the specification fails to disclose a therapeutic composition which comprises, comprising "all possible" mutant IL-15 polypeptides fused to the Fc region of an immunoglobulin, and an IL-2 polypeptide fused to the Fc region of an immunoglobulin. While the instant specification demonstrates that IL-2/Fc molecule lyses IL-2R bearing CTLL-2 cells and while the specific mutant IL-15/Fc (mutated at positions 149 and 156 of the wild type IL-15) chimera binds IL-15R and blocks IL-15 activities, the specification fails to disclose that "all" possible IL15/Fc mutants would also retain the desired activity.

The criteria set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, is the basis for determining undue extermination. In the instant application, it will be undue experimentation to make a therapeutic compositions that comprise a first agent that comprises "all possible" IL-15 mutants fused to Fc, test whether each and every IL-15 mutant retains the desired activity of binding to IL-15R but blocks the IL-15 activities, and a second agent which comprises IL-2 polypeptide fused to Fc region. The quantity of experimentation to determine which IL-15 mutants retain the desired activity, are practically infinite and the guidance provided in the specification very little. Therefore, the instant specification is not enabling for a therapeutic composition comprising a first agent that comprises "all possible" mutant IL-15 polypeptides that bind to an IL-15R but fails to fully activate signal transduction, optionally fused to the Fc region of an immunoglobulin, and a second agent that comprises an IL-2 polypeptide that is optionally fused to the Fc region of an immunoglobulin.

Response to Applicants' Arguments Regarding Enablement Rejection:

Applicants argue that they have taught how to make and use the first and second agents recited in the present claims, and there is no reason why one of ordinary skill in the art could not now do the same. Applicants further submit that IL-15 and IL-2 are not

new polypeptides, they are well known in the art and can be made using routine molecular biology techniques. It is well within the abilities of one of ordinary skill in the art to make and use the agents now recited in the claims; the level of skill in the art is high and that some experimentation is permitted.

This is fully considered but is not deemed persuasive. It is acknowledged that IL-15 and IL-2 are not new polypeptides. The instant claims require specific activity to be retained, i.e, that the IL-15 mutant should bind to IL-15R and also not activate signal transduction, however, both the instant and the cited prior art disclose only one specific such mutant, said mutant having specific mutations at amino acid residues 149 and 156 which retains the desired activity, (see claims of U.S. Patent 6,001,973). Furthermore, It is known for proteins that even a single amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the disclosure of one IL-15 mutant that displays a specific function does not provide support regarding enablement for "all" possible IL-15 mutants. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequences may be found to be conserved over biomolecules of related function upon a significant amount of further research (see Wells, 1990; Biochemistry 29:8509-8517). Moreover, site directed mutagenesis of IL-15 could result in mutants that act as antagonists (an activity required by the instant claims) as well as agonists, (see Bernard et al, The Journal of Biological Chemistry, June 2004, Vol. 279, No. 23, pages 24313-24322). Bernard et al teach that

mutations at positions Leu-45 (L45D and L45E), Ser-51 and Leu-52 reproducibly in an increased affinity of IL-15 in competition assay. Accordingly, the disclosure of a single IL-15 mutant does not satisfy the enablement requirement for "all" possible IL-15 mutants that retains a specific activity. Finally, it is acknowledged that the level of skill in the pertinent art is quite high, i.e. generally a PhD in biochemistry, however, to practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve designing IL-15 mutants and test them for the retention of the desired activity. It is this additional characterization of the disclosed composition that is required in order to obtain the functional and structural data needed to permit one to produce a therapeutic composition which meets both the structural and functional requirements of the instant claims that constitutes undue experimentation.

2b. Claim 1 stands rejected and new claims 35-36, 42-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons of record set forth in the previous office action.

Applicants argue that amended claim 1 recites each of the required agents and that claim 1 now requires that the first agent include a mutant IL-15 polypeptide and further recites a functional limitation that must be fulfilled by that polypeptide. Claim 1 now also requires that the second agent include an IL-2 polypeptide. As described in the specification, either of these polypeptides can be fused to the Fc region of an immunoglobulin. Applicants further submit that IL-15, IL-2, and Fc regions of

immunoglobulins were known in the art at the time the present application was filed, thus, the present specification would have conveyed to one of ordinary skill in the art that the present inventors, at the time their application was filed, had possession of compositions containing the agents now claimed.

This argument has been considered but is not found persuasive. The instant specification and the prior art disclose a single IL-15 mutant, one which that has mutations at positions 149 and 156 of the wild type IL-15, wherein a glutamine is replaced with an aspartic acid, fused to the Fc region of immunoglobulin, said mutant which displays specific activity. However, the disclosure of one mutant does not provide written description for "all" possible IL-15 mutants that retain the desired activity, nor does it provide written description to IL-15 mutant polypeptide that is at least 90% identical to wild-type IL-15 which also retains the specific desired activities.

New Rejections:

Claim rejections-35 USC § 112, First Paragraph, New Matter:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3a. Claims 1 and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 1 and 45 recite, in lines 4 and 3,

respectively, ".....binds an IL-15R but fails to fully activate signal transduction through the IL-15R...", ...", however, said language is new matter and has no support in the instant specification as originally filed. The specification on page 11, lines 30-31 discloses "...the targeting moiety binds an IL-15R without effectively transducing a signal through that receptor...", however, this language differs from the language recited in the claims, because the supported language is interpreted as meaning that there is no signal through the IL-15R, while the claimed language implies that there might be partial signal transduction.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

4. Claims 1, 35-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4a. Claims 1 and 45 in lines 4 and 3, respectively, recite ".....but fails to fully activate signal transduction through the IL-15R...", which renders the claims indefinite, because the specification fails to describe the meaning of this phrase. Does this mean that there is no signal transduction through the IL-15R or partial signal transduction, if partial inhibition is desired, than how much, 50% more or less? The metes and bounds of the claims cannot be ascertained. Appropriate correction is required.

4b. Claim 44, in line 3 recites "....is a target-cell deleting FC regions", however, it is not clear what is a target-cell deleting FC regions. Clarification is required.

Claims 35-43 and 46 are rejected under 35 U.S.C. 112, second paragraph, so long as they depend on claims 1 and 45, for the limitation set forth directly above.

Claim rejections-35 USC § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5a. Claims 1 and 35-46 are rejected under 35 U.S.C. 103(a) as being unpatentable Kim et al (16/998) in view of Strom et al (1995).

The instant claims are drawn to a therapeutic composition comprising a first agent that comprises or consists a mutant IL-15 polypeptide, optionally fused to the Fc region of an immunoglobulin, and a second agent that comprises or consists an IL-2 polypeptide that is optionally fused to the Fc region of an immunoglobulin said IL-15 mutant having a substitution of aspartate for glutamine at positions 149 and 156 of the wild type IL-15, and wherein said IL-15 mutant binds an IL-15Rα of an IL-15R.

Kim et al teach a IL-15 mutant/Fcγ2a, wherein aspartic acid at positions 101 and 108 of the mature wild type IL-15 (which corresponds to amino acids 149 and 156, respectively of the full length IL-15 including the signal sequence which contains 48 amino acid residues) are substituted with glutamine, said IL-15 mutant which is then fused to Fc region of IgG to overcome short half life, (see page 5742, column 2). Kim et al show that the IL-15mutant/ Fcγ2a binds specifically to IL-15Rα, antagonizes the IL-15 receptor, and inhibits T cell proliferation (see abstract, page 5744 and figures 2 and 3). The IL-15 mutant/ Fcγ2a antagonist also markedly attenuated Ag-specific delayed type hypersensitivity and decreased leukocyte infiltration and also exhibits prolonged half life.

However, Kim et al do not teach a therapeutic composition comprising a first agent that comprises or consists a mutant IL-15 polypeptide, optionally fused to the Fc region of an immunoglobulin, and a second agent that comprises or consists an IL-2 polypeptide that is optionally fused to the Fc region of an immunoglobulin said IL-15 mutant having a substitution of aspartate for glutamine at positions 149 and 156 of the wild type IL-15, and wherein said IL-15 mutant binds an IL-15Rα of an IL-15R.

Strom et al teach a fusion protein which comprises IL-2 fused to Fc region of immunoglobulin and teaches that said chimera is cytolytic and retains in vivo efficacy as an immunosuppressive agent, (see pages 19-20). Strom et al teach that the IL-2Fcγ2a chimera maintains the structural and functional integrity of both the IL-2 and Fc moieties, and further exhibits a 30 fold increase half life compared to IL-2 by itself, (see page 20).

Therefore, It would have been prima facie obvious at the time of the instant invention, to device a composition comprising the IL-15 mutant/ Fcγ2a antagonist taught by Kim et al and the IL-2Fcγ2a fusion protein taught by Strom et al, because Kim et al teach that their fusion protein binds to the IL-15R and competitively inhibits IL-15 triggered cell proliferation, while Strom et al teach that their IL-2Fcγ2a chimera is cytolytic and functions as an immunosuppressive agent. There would have been a great expectation of success that combing the IL-15 mutant/ Fcγ2a taught by Kim et al and the IL-2Fcγ2a chimera taught by Strom et al, would result in a therapeutic agent, because each is taught in the prior art to be useful for the same purpose, i.e, as an immunosuppressive agent, *In re Kerkhoven, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980).* One of ordinary skill in the art would have been motivated to combine the teachings of Kim et al and Strom et al, because each reference teaches an agent for the treatment of autoimmune diseases or organ transplantation, and it flows logically that the combined composition would be expected to be useful in the treatments of said diseases.

Conclusion

6. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M. Hamud whose telephone number is (571) 272-0884. The examiner can normally be reached on Monday, Thursday-Friday, 6:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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25 January 2007

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